Short Access to Belt Compounds with Spatially Close C=C Bonds and Their Transannular Reactions

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In memory of Jean-Paul Picard

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ABSTRACT:

Two domino Diels–Alder adducts were obtained from 3,7-bis(cyclopenta-2,4-dien-1-ylidene)-cis-bicyclo[3.3.0]octane and dimethyl acetylenedicarboxylate or Nmethylmaleimide under microwave irradiation. From the first adduct, a C20H24 diene with C2v symmetry was obtained by Zn/AcOH reduction, hydrolysis, oxidative decarboxylation, and selective hydrogenation. Photochemical [2+2] cycloaddition of this diene gave a thermally unstable cyclobutane derivative, which reverts to the diene. However, both the diene and the cyclobutane derivatives could be identified by X-ray diffraction analysis upon irradiation of the diene crystal. New six-membered rings are formed upon the transannular addition of bromine or iodine to the diene. The N-type selectivity of the addition was examined by theoretical calculations, which revealed the distinct susceptibility of the doubly bonded carbon atoms to the bromine attack.

INTRODUCTION

Pyramidalized alkenes contain C=C double bonds in which one or both of the doubly bonded carbon atoms do not lie in the same plane as the attached atoms.[1] The degree of pyramidalization of these carbon atoms may be large enough to confer unique structural, spectroscopic, and chemical properties.[2] In this context, we have reported the generation, trapping as Diels–Alder (DA) adducts and dimerization of the highly pyramidalized alkenes 2, containing the tricyclo[3.3.0.03,7]oct-1(5)- ene skeleton (Scheme 1).[3] Of particular interest is the formation of cyclobutane dimers, which experience a thermal [2+2] retrocycloaddition to the belt dienes 4 with close parallel C=C bonds.[3g] In turn, these compounds photochemically generate the cyclobutane products and experience transannular additionsof electrophiles, such as bromine, iodine, or water.

Because the preparation of the diiodides 1 implies many synthetic steps, the dienes 4 are not readily available. Herein, we describe a short synthetic route to the dienes 8 and 9 (Scheme 2), which features a key step consisting of a domino DA reaction among the known[4] difulvene 7 and dimethyl acetylenedicarboxylate or N-methylmaleimide under microwave irradiation. Furthermore, several transannular and photochemical transformations of these compounds are also examined. The preferential formation of N-type halogenated adducts over the U-type products is investigated by means of theoretical calculations. Overall, the results support the reliability of the domino Diels–Alder reaction to yield polycyclic compounds with belt structures having close parallel C=C bonds.

RESULTS AND DISCUSSION

Reaction of equimolar amounts of the difulvene 7 and dimethyl acetylenedicarboxylate in 1,2-dichlorobenzene under microwave irradiation at 150 8C for 5 min gave a product mixture, which after column chromatography and washing with MeOH yielded the domino DA adduct 8 in 24% yield (Scheme 2). Longer or shorter reaction times of microwave irradiation led to lower yields of compound 8.

Similarly, reaction of compound 7 with N-methylmaleimide under similar conditions and treatment gave adduct 9 in only 11% yield (Scheme 2). Alternatively, compound 9 was obtained by microwave irradiation of a mixture of the double DA adducts of the difulvene 7 and N-methylmaleimide in 1,2-dichlorobenzene. The formation of compound 9 under these conditions requires that the above-described double DA adducts experience a retro-DA reaction to regenerate the fulvene subunit necessary for the intramolecular DA reaction.

Worthy of note, reaction of compound 7 and maleic anhydride or cis- and trans-1,2-bis(phenylsulfonyl)ethylene, under microwave irradiation conditions used to prepare compound 8, did not give any defined product. This agrees with the findings by Hong et al.[5] who reported that the reaction of 7,7-dimethylfulvene and maleic anhydride under microwave irradiation did not give the expected DA addition product, but adducts from tautomeric derivatives of the fulvene unit. In this work, the expected DA adducts were formed under conventional thermal conditions.

Hydrogenation of the products 8 and 9 by using 5% Pd on charcoal led to the selective formation of compounds 10 and 11, respectively.[6] The configuration of all of these compounds was clearly established by spectroscopic studies and, for compounds 8, 9, and 10, confirmed by X-ray diffraction analysis (see the Supporting Information). Compound 10 was irradiated in a quartz reactor by using a 125W medium-pressure mercury lamp in pentane[3c] or in a 1:1 benzene/acetone[7] mixture at different reaction times (till 24 h). Due to solubility problems, compound 11 was irradiated under similar conditions but only in a 1:1 benzene/acetone mixture. In both cases, there was no evidence supporting the formation of cyclobutane derivatives, even though the starting compounds were degraded.

Because the failure of the intramolecular [2+2] photocycloaddition process might be due to the ester or imide groups, the tetraene 17 was prepared (Scheme 3). Reduction of the diester 8 with Zn/AcOH[8] under ultrasonic irradiation gave a stereoisomeric mixture of the esters 12, 13, and 14, in a ratio 12/13/14 close to 3:4:1, as confirmed by 1H NMR spectroscopy, which could be partially separated by silica gel column chromatography, thus obtaining samples of each stereoisomer. Assignment of the endo,endo-stereoisomer 13 was confirmed upon hydrogenation, yielding the expected diester 10. Next, the stereoisomeric mixture of the diesters 12, 13, and 14 was hydrolyzed[7] to give mainly the corresponding endo,exo-diacid 15, which contains a norbornane substructure. Following Paquette et al.,[9] oxidative decarboxylation of the diacid 15, was only attempted by using either electrolysis or Cu2O oxidation in quinoline at high temperature. Electrolysis of the diacid 15 was carried out in a 9:1 pyridine/water mixture as solvent in the presence of triethylamine.[8, 10] However, both NMR and Xraydata (see the Supporting Information) confirmed that the only defined product isolated from this reaction was the alcohol 16 (4 %), which might have been formed by hydration of the tetraene 17. Fortunately, oxidative decarboxylation of the diacid 15 by using Cu2O[9] gave the high melting point C2v-symmetric C20H20 tetraene 17 (16%) together with significant amounts of 2-methylnaphthalene and traces of 1-methylnaphthalene as byproducts. The structure of compound 17 was confirmed by X-ray diffraction analysis (see the Supporting Information).

Selective hydrogenation of the tetraene 17 led to the diene 18 (Scheme 4). Irradiation of compound 17 (quartz reactor, 125W medium-pressure mercury lamp in pentane[3c] or in a 1:1 benzene/acetone[7]

mixture) at different reaction times (till 4 h) led to degradation products in which the olefinic protons had disappeared. GC-MS showed the presence, among others, of dihydro and tetrahydro compounds.

However, irradiation of the diene 18 in pentane with the same lamp for 3 h led to a mixture of the cyclobutane 19 and minor amounts of compound 18. The 1H and 13C NMR data of compound 19 could be obtained from the spectra of its mixture with the diene 18. The thermal conversion of the cyclobutane 19 to the diene 18 was followed by 1H NMR spectroscopy in CDCl3 at 25, 35, and 458C (see Table S1 in the Supporting Information), revealing first-order kinetics. The following rate constant values were obtained: k25=0.0030, k35=0.0112, and k45=0.0231 min¢1. By using the Arrhenius equation, an activation energy of 19.2 kcalmol¢1 and a pre-exponential Arrhenius factor of 3.4·1011 min¢1 were calculated. The activation energy of this process compares with the value of 22.7 kcalmol¢1 for the conversion of the more stable cyclobutane 3a to the corresponding diene 4a in CDCl3.[3b] Irradiation of a crystallographic sample of compound 18 gave a new crystal, containing molecules of the cyclobutane 19 and the diene 18 in a 19/18 ratio of about 1:1. The atom site occupancy for the olefinic carbon atoms of compound 18 and the cyclobutane carbon atoms of compound 19 was 0.500 for all of them. The X-ray data showed that the monoclinic crystal state of compound 18 had been retained during the irradiation process. All the atoms, except the olefinic carbon atoms of compound 18, retained their position in its conversion to compound 19 (see the Supporting Information). Figure 1 shows the ORTEP representation of the mixture of compounds 19 and 18. The easy thermal opening of the cyclobutane 19 to the diene 18, whether during irradiation of the crystal or during acquisition of the X-ray data, and not the size of the crystal, might be the reason why no pure cyclobutane 19 was observed in the X-ray experiment.

Photochemical transformations in the solid state are well known, sometimes accompanied by photochromism.[11, 12] However, to the best of our knowledge, no intramolecular [2+2] photocycloaddition of simple alkenes in the solid state and in the absence of any photosensitizer has been reported before.

The olefinic carbon atoms of compounds 8, 9, 10, 17, and 18 are slightly pyramidalized: C4/C9 (13.5–15.88) and C3a/C9a (2.0–5.88).[13] Also, the C6¢C7 (1.586–1.589 æ) and C13¢C14 bonds (1.572–1.588 æ) are somewhat longer than the standard C¢C bond length (see Table S2 in the Supporting Information).

Reaction of the diene 18 with a slight molar excess of bromine or iodine in CH2Cl2 gave compounds 21 and 22, respectively, as the only detected products (Scheme 4). The 13C NMR data supported the Cs symmetry group (N-type addition). Utype additions would have generated a five- and a sevenmembered ring in the halogenated products, leading to products with C2v symmetry. X-ray diffraction analyses further confirmed the structures of compounds 21 and 22 (see in Supporting Information).

The mechanism of the bromination addition of the diene 18 was examined by combining density functional theory calculations and the self-consistent reaction field theory to account for solvation effects. DFT calculations were performed by using the M062X/6-31+G(d)[14] level of theory, and solvation effects in CH2Cl2 were accounted for with the solvation model based on the solute electron density (SMD) method.[15] The geometries were fully optimized and the nature of the stationary points was verified by determination of the vibrational frequencies (see the Supporting Information). The structural parameters derived from the optimized geometry of compound 18 showed a close agreement with the X-ray structure, as noted in the pyramidalization of the C=C carbon atoms (C3a/ C9a: 4.88, C4/C9: 15.68), and the lengths of the C6¢C7 and C13¢C14 bonds (1.581 and 1.582 æ, respectively).

In the pre-reactant complex (i.e., I1 in Figure 2), the bromine atom closest to the molecule is roughly equidistant (2.37–2.50 æ) from the doubly bonded carbon atoms. Addition of bromine to the carbon atoms C3a and C4 is concurrent with the breaking of the bond in the Br2 molecule and with the formation of bonds between the atom pairs C4¢C9a and C3a¢C9 (distances of 2.48 and 2.12 æ,

respectively, in the transitionstate structures (i.e., TS(3a) and TS(4) in Figure 2). The barrier for the addition to the C3a atom is approximately 3.2 kcal mol¢1 more favorable than the addition to the C4 atom. This difference can be partly ascribed to the larger electron density supported by the C3a atom relative to the C4 atom in the diene (Dq=0.034 e, Figure S1 in the Supporting Information). This process leads to a N-type-brominated adduct cation, which is characterized by the presence of internal six-membered rings leading to a formal positive charge on the carbon atom C9. Finally, the nucleophilic addition of the bromine anion to the C9 atom generates compound 21. All attempts to locate the transition states leading to the U-type bromine addition were unsuccessful, suggesting that this process induces a larger structural barrier than the N-type addition. The largest destabilization of the U-type adduct formed upon addition to the C4 atom is reflected in the relative free energy compared to the N-type adducts, because the former is destabilized by around 15 kcalmol¢1 relative to the preferred N-type-brominated cation adduct (i.e., I3(3a) in Figure 3). This trend is also noted in the larger distance between the carbon atoms of the bond formed between the two C=C bonds, and the lower value of the electron density at the bond critical point (Figure 3). In addition, all attempts to locate the U-type adduct originating from bromination at the C3a atom failed.

Bromination of the diene diester 10 was performed under similar conditions, leading to a mixture of the isomeric dibromides 23 and 24. Samples of these dibromides could be obtained by slow crystallization from EtOAc and were fully characterized by spectroscopic and analytical means including Xray diffraction analysis. As before, only N-type addition was observed. Compound 23 was the major species of the reaction mixture, which contained compounds 23 and 24 in a ratio of 3.5:1 (as obtained by 1H NMR spectroscopy), an effect that can be ascribed to the inductive effect of the ester groups on the double bond formed by the C3a and C4 atoms.

The X-ray diffraction data for most compounds described in this paper have been collected in the Tables S3 and S4 in the Supporting Information. CCDC 1400938 (8), 1400939 (9), 1400940 (10), 1400941 (16), 1400942 (17), 1400943 (18),1400944 (19), 1400945 (21), 1400946 (22), 1400947 (23), and 1400948 (24) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

CONCLUSIONS

In summary, the domino Diels–Alder reaction of 3,7-bis(cyclopenta-2,4-dien-1-ylidene)-cis-bicyclo[3.3.0]octane and dimethyl acetylenedicarboxylate has been shown to be a short route to polycyclic compounds with belt structures having close parallel C=C bonds that experience different transannular processes.

EXPERIMENTAL SECTION

General information

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp melting-point apparatus. All new compounds were fully characterized by their analytical (melting point, elemental analysis, and/or accurate mass measurement, spectroscopic data (IR, 1H NMR, and 13C NMR) and in much cases Xray diffraction analysis. Assignments given for the NMR spectra are based on DEPT, COSY, 1H/13C single quantum correlation (Ghsqc sequence), and 1H/13C multiple bond correlation (gHMBC sequence) spectra. 1H NMR and 13C NMR spectra were recorded on a Varian Mercury 400 (400 MHz for 1H, 100.6 MHz for 13C) spectrometer. Unless otherwise stated, NMR measurements have been performed in CDCl3. Chemical shifts (d) are reported in parts per million related to TMS or CDCl3 as internal standard. Multiplicities are reported by using the following abbreviations: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad or their combinations. IR spectra were registered on a FTIR Perkin–Elmer Spectrum RX1 spectrometer by using the attenuated total reflectance (ATR) technique. Absorption values are given as wavenumbers, the intensity of the absorptions is given as strong (s), medium (m), or weak (w). High-resolution mass spectrometry (HRMS) were carried out at the Mass Spectrometry Unity of the Centres Cient†fics i Tecnolýgics of the Universitat de Barcelona (CCiTUB) and the results are reported as m/z. Except for compound 22 a LC/MSD-TOF spectrometer with electrospray ionization (ESI-TOF-MS) from Agilent Technologies was used. The HRMS of compound 22 was performed on a LTQ Orbitrap Velos mass spectrometer (Thermo Scientific, Bremen, Germany). The elemental analyses were carried out at the IIQAB (CSIC) of Barcelona, Spain, in an elemental microanalyzers (A5) model Flash1112 series from Thermofinnigan for (C, H, and N) determinations, and in a titroprocessor Methrom model808 for the halogen determination. Microwave irradiation experiments were performed by using a single-mode discover system from CEM Corporation by using standard Pyrex vessel (capacity of 10 mL). For the flash column chromatography, silica gel 60AC (35–70 mm, SDS, ref. 2000027) was used. The eluents employed are reported as volume/volume percentages. Thin-layer chromatography (TLC) was performed on aluminum-backed sheets with silica gel 60F254 (Merck, ref. 1.05554) and spots were visualized with UV light or a 1% aqueous solution of KMnO4. X-ray diffraction analyses were performed in a D8 Venture diffractometer at the CCiTUB of the University of Barcelona. The diketone 6 was prepared as described[16] from glioxal (40% in water) and dimethyl 1,3-acetonedicarboxylate, both obtained from Sigma–Aldrich. Dimethyl acetylenedicarboxylate, copper(I) oxide, and 2,2'-bipyridyl were purchased from Sigma–Aldrich, N-methylmaleimide from TCI, zinc powder from Panreac, neutral aluminum oxide Brockman I (50–200 mm) from Acros Organics, and 5% Pd/C from Degussa AG. All chemicals were used without further purification.

Dimethyl (3R,3aZ,6S,7R,9Z,10S,12aR,13S,13aS,14R)-5,6,7,8,10,12a,13,13a-octahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylate (8)

A solution of the difulvene 7 (300 mg, 1.28 mmol) and dimethyl acetylenedicarboxylate (0.16 mL, 98%, 181 mg, 1.28 mmol) in 1,2- dichlorobenzene (4 mL) was placed in a 10 mL microwave tube, which was closed and irradiated at 1508C for 5 min. This process was repeated seven times more, by using compound 7 (total amount: 2.44 g, 10.4 mmol). The combined solutions were concentrated in vacuum and the yellow brown residue (…4 g) was subjected to column chromatography (35–70 mm silica gel (96 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 85:15, a mixture of the domino DA adduct 8 and adducts still containing a fulvene subunit (931 mg) was isolated as yellow solid. After washing this solid with MeOH (4 mL), compound 8 was obtained as light yellow solid (794 mg, 24% yield). M.p. 185–1868C (decomp.) (MeOH); 1H NMR (400 MHz, CDCl3): d=1.91 (s, 2H; 13(14)-H),

2.08 (d, 2J(H,H)=12.8 Hz, 2H) and 2.09 (d, 2J(H,H)= 12.4 Hz, 2H) (5(15)-Hb and 8(16)-Hb), 2.21 (dd, 2J(H,H)=12.6, 3J(H,H)=3.6 Hz, 4H; 5(15)-Ha, 8(16)-Ha), 2.46–2.52 (m, 2H, 6(7)-H), 3.07 (t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 10(12a)-H), 3.42 (s, 2H, 3(13a)- H), 3.76 (s, 6H, 2ÕOCH3), 6.39 ppm (t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 11(12)-H); 13C NMR (100.6 MHz, CDCl3): d=36.3 [CH, C6(7)], 40.2 [CH2, C5(15), C8(16)], 45.3 [CH, C10(12a)], 46.3 [CH, C13(14)], 49.1 [CH, C3(13a)], 51.9 (CH3, OCH3), 124.1 (C, C9), 128.1 (C, C4), 135.8 (C, C3a), 140.3 (C, C9a), 140.3 [CH, C11(12)], 147.8 [C, C1(2)], 164.9 ppm (C, COOCH3); IR (ATR): n˜=2992 (w), 2948 (m), 2914 (w), 2842 (w), 1736 (s), 1714 (s), 1433 (m), 1306 (s), 1287 (m), 1205 (s), 1192 (s), 1168 (s), 1114 (m), 1094 (s), 1026 (s), 803 (m), 693 cm¢1 (s); accurate mass measurement: m/z calcd for C24H24O4+H+: 377.1747; found: 377.1742; elemental analysis calcd (%) for C24H24O4·0.5H2O: C 74.78, H 6.54; found: C 74.57, H 6.54.

N-Methyl (1R,2S,3R,3aZ,6S,7R,9Z,10S,12aR,13S,13aS,14R)- 5,6,7,8,10,12a,13,13a-octahydro-3H-3,10,13-(epimethanetriyl)- 4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboximide (9)

Procedure 1: A solution of the difulvene 7 (300 mg, 1.28 mmol) and N-methylmaleimide (142 mg, 1.28 mmol) in 1,2-dichlorobenzene (4 mL) was placed in a 10 mL microwave tube, which was closed and irradiated at 1508C for 5 min. The solution was concentrated in vacuum and the brown residue was subjected to column chromatography (35–70 mm silica gel (55 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 95:5, the difulvene 7 (31 mg) was isolated as yellow solid. On elution with hexane/EtOAc 80:20 and 75:25, the domino DA adduct 9 (64 mg) was isolated as a beige solid. After washing this solid with MeOH (0.7 mL), the pure compound 9 was obtained as a white solid (48 mg, 11% yield).

Procedure 2: A solution of the difulvene 7 (2.07 g, 8.83 mmol) and N-methylmaleimide (2.94 g, 26.5 mmol) in toluene (40 mL) was stirred at room temperature for 110 h in a closed flask fitted with a gas outlet. The solution was concentrated in vacuum and the yellow brown residue (5.03 g) was subjected to column chromatography (35–70 mm silica gel (100 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 2:3, a stereoisomeric mixture of the double DA adducts (3.75 g, 93% yield) was isolated as white solid. A part of this mixture (300 mg, 0.66 mmol) in 1,2-dichlorobenzene (4 mL) was placed in a 10 mL microwave tube, which was closed and irradiated at 1508C for 5 min. This process was repeated twelve times more (total amount of the double DA mixture: 3.58 g, 7.78 mmol). The combined solutions were concentrated in vacuum and the yellow brown residue (4.62 g) was subjected to column chromatography (35–70 mm silica gel (50 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 4:1 and 3:1 the domino DA adduct 9 (445 mg, 16% yield) was isolated as a white solid. Crystallization of a sample of compound 9 (290 mg) from EtOAc (15 mL) gave an analytical sample of compound 9 (113 mg) as a white crystalline solid. M.p. 254–2558C (decomp.) (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.53 (s, 2H; 13(14)-H), 2.05 (d, 2J(H,H)=12.8 Hz, 2H; 8(16)-Hb), 2.06 (d, 2J(H,H)=12.8 Hz, 2H; 5(15)-Hb), 2.13–2.21 (m, 4H; 5(15)-Ha, 8(16)-Ha), 2.38–2.45 (m, 2H; 6(7)-H), 2.63 (s, 2H; 1(2)-H), 2.83 (s, 3H; N-CH3), 2.98 (s, 2H; 3(13a)-H), 3.13 (t, 3J(H,H)=4J(H,H)= 2.0 Hz, 2H; 10(12a)-H), 6.30 ppm (t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 11(12)-H); 13C NMR (100.6 MHz, CDCl3): d=24.5 (CH3, N-CH3), 35.6 [CH, C6(7)], 40.0 [CH2, C8(16)], 40.9 [CH2, C5(15)], 43.6 [CH, C13(14)], 44.6 [CH, C3(13a)], 46.3 [CH, C10(12a)], 49.4 [CH, C1(2)], 124.0 (C, C9), 128.3 (C, C3a), 136.0 (C, C4), 138.6 [CH, C11(12)], 139.5 (C, C9a), 178.2 ppm (C, CON); IR (ATR): n˜=2984 (w), 2837 (w), 1769 (w), 1692 (s), 1435 (m), 1380 (m), 1299 (m), 1281 (m), 1131 (m), 1111 (m), 971 (m), 738 (m), 687 (m), 646 cm¢1 (m); accurate mass measurement: m/z calcd for C23H23NO2+H+: 346.1802; found: 346.1792; elemental analysis calcd (%) for C23H23NO2·2H2O: C 72.42, H 7.13, N 3.67; found: C 72.60, H 6.82, N 3.39.

Dimethyl (1R,2S,3R,3aZ,6S,7R,9Z,10R,12aS,13R,13aS,14S)-2,3,5,6,7,8,10,11,12,12a,13,13a-dodecahydro-1H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylate (10)

A suspension of compound 8 (191 mg, 0.51 mmol) and 5% Pd on charcoal (50% in water, 19 mg) in EtOAc (20 mL) was hydrogenated at room temperature and atmospheric pressure for 3 h. The suspension was filtered through a short pad of celite and concentrated in vacuum to give the crude compound 10 as a white solid (177 mg, 96% yield). An analytical sample of compound 10 (42 mg) was obtained as a white crystalline solid by crystallization of a part of this product (114 mg) from EtOAc (2 mL). M.p. 192–1948C (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.27–1.32 (m, 2H; 11(12)-Hendo), 1.44–1.50 (m, 2H; 11(12)-Hexo), 2.05 (s, 2H; 13(14)-H), 2.18 (d, 2J(H,H)=12.8 Hz, 2H) and 2.19 (d, 2J(H,H)=12.4 Hz, 2H) (5(15)-Hb and 8(16)-Hb), 2.23–2.28 (m, 4H; 5(15)-Ha, 8(16)-Ha), 2.40–2.46 (m, 2H; 6(7)-H), 2.42 (t, 3J(H,H)=4J(H,H)=2.2 Hz, 2H; 10(12a)-H), 2.83 (dd, 3J(H,H)=2.4, 4J(H,H)=2.0 Hz, 2H; 3(13a)-H), 2.91 (dd, 3J(H,H)=2.4, 4J(H,H)=1.6 Hz, 2H; 1(2)-H), 3.66 ppm (s, 6H; 2 OCH3); 13C NMR (100.6 MHz, CDCl3): d=29.3 [CH2, C11(12)], 35.3 [CH, C6(7)], 40.9 (CH2) and 41.0 (CH2) [C5(15) and C8(16)], 41.1 [CH, C13(14)], 41.25 [CH, C10(12a)], 45.3 [CH, C3(13a)], 46.6 [C, C1(2)], 51.4 (CH3, OCH3), 127.8 (C, C9), 130.8 (C, C4), 133.25 (C, C3a), 139.1 (C, C9a), 172.6 ppm (C, COOCH3); IR (ATR): n˜=2961 (w), 2942 (m), 2928 (m), 2839 (w), 1744 (s), 1739 (s), 1429 (m), 1356 (m), 1344 (m), 1181 (s), 1156 (s), 1142 (s), 1111 (m), 1081 (m), 1069 (m), 1052 (s), 921 (m), 821 (m), 761 (m), 743 cm¢1 (m); accurate mass measurement: m/z calcd for C24H28O4+H+: 381.2060; found: 381.2063; elemental analysis calcd (%) for C24H28O4: C 75.76, H 7.42; found: C 75.65, H 7.57.

N-Methyl (1R,2S,3S,3aZ,6R,7S,9Z,10S,12aR,13S,13aR,14R)-2,3,5,6,7,8,10,11,12,12a,13,13a-dodecahydro-1H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboximide (11)

A mixture of the imide 9 (424 mg, 1.23 mmol) and 5% Pd on charcoal (50% in water, 45 mg) in CH2Cl2 (40 mL) was hydrogenated at room temperature and atmospheric pressure for 3 h. The mixture was filtered through a short pad of celite and concentrated in vacuum to give the product 11 (406 mg, 95% yield) as a white solid. An analytical sample of compound 11 was obtained by crystallization of a part of the crude product (104 mg) from EtOAc (4.5 mL), thus obtaining compound 11 (54 mg) as a white crystalline solid. M.p. 245–247 8C (EtOAc); 1H NMR (400 MHz, CDCl3): d= 1.21–1.26 (m, 2H; 11(12)-Hendo), 1.48–1.55 (m, 2H; 11(12)-Hexo), 1.60 (s, 2H; 13(14)-H), 2.09 (d, 3J(H,H)=12.8 Hz, 2H; 5(15)-Hb), 2.14 (d, 2J(H,H)=12.8 Hz, 2H; 8(16)-Hb), 2.14–2.21 (m, 2H; 5(15)-Ha), 2.21– 2.26 (m, 2H; 8(16)-Ha], 2.38–2.44 [m, 2H; 6(7)-H), 2.50 (dd, 3J(H,H)= 2.4, 4J(H,H)=2.0 Hz, 2H; 10(12a)-H), 2.62 (s, 2H; 1(2)-H), 2.82 (s, 3H; N-CH3), 2.92 ppm (s, 2H; 3(13a)-H); 13C NMR (100.6 MHz, CDCl3): d=24.5 (CH3, N-CH3), 29.3 [CH2, C11(12)], 35.1 [CH, C6(7)], 40.8 [CH2, C8(16)], 40.9 [CH2, C5(15)], 41.1 [CH, C10(12a)], 45.2 [CH, C3(13a)], 45.9 [CH, C13(14)], 48.9 [CH, C1(2)], 128.3 (C, C3a), 128.9 (C, C9), 136.0 (C, C4), 136.6 (C, C9a), 178.5 ppm (C, CON); IR (ATR): n˜=2951 (m), 2914 (w), 2857 (w), 2836 (w), 1767 (w), 1693 (s), 1679 (s), 1434 (m), 1380 (m), 1300 (m), 1280 (m), 1131 (m), 1108 (m), 972 (m), 643 (m), 630 cm¢1 (m); accurate mass measurement: m/z calcd for C23H25NO2+H+: 348.1958; found: 348.1949; elemental analysis (%) calcd for C23H25NO2: C 79.51, H 7.25, N 4.03; found: C 79.52, H 7.40, N 3.93.

Dimethyl (1RS,2RS,3RS,3aZ,6SR,7RS,9Z,10RS,12aSR,13RS, 13aSR,14SR)-1,2,5,6,7,8,10,12a,13,13a-decahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylate (12), (1R,2S,3R,3aZ,6S,7R,9Z,10R,12aS,13R,13aS,14S)-1,2,5,6,7,8,10,12a,13,13a-decahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylate (13), and (1R,2S,3S,3aZ,6R,7S,9Z,10S,12aR,13-S,13aR,14R)-1,2,5,6,7,8,10,12a,13,13a-decahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylate (14)

Zn dust (347 mg, 5.31 mmol) was added to a suspension of the diester 8 (250 mg, 0.66 mmol) in glacial AcOH (3.5 mL), and the mixture was submitted to ultrasonic irradiation at room temperature for 2 h in a closed flask fitted with a gas outlet. The reaction mixture was filtered through a short pad of CeliteÒ and concentrated in vacuum to give a light brown semisolid residue (247 mg), which was subjected to column chromatography (35–70 mm silica gel (15 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 97:3, compound 12 (22 mg) was isolated as a white solid. On elution with hexane/EtOAc 96.5:3.5, a mixture of compounds 12 and 13 (88 mg, ratio 1:1.3 determined by 1H NMR spectroscopy) and the pure compound 13 (28 mg) were isolated, both as white solids. On elution with hexane/EtOAc 9:1, compound 14 (22 mg) was isolated as a white solid (global yield, 160 mg, 64 %). The mixture of compounds 12 and 13 (88 mg) was subjected to a new column chromatography (35–70 mm silica gel (15 g), hexane/EtOAc mixtures). On elution with hexane/EtOAc 97:3, compound 12 (19 mg) and a mixture of compounds 12 and 13 (37 mg, ratio 1:2 determined by 1H NMR spectroscopy) were isolated as white solids. On elution with hexane/EtOAc from 97:3 to 95:5, the pure compound 13 (23 mg) was isolated as a white solid. Crystallization of samples of compounds 13 (28 mg), 12 (22 mg), and 14 (22 mg) from EtOAc (0.5 mL) gave the corresponding analytical samples (13, 10, and 10 mg, respectively).

Analytical and spectroscopic data of compound 12: White solid; m.p. 192–1938C (EtOAc), at 186–1888C the sample of compound 12 becomes a paste; 1H NMR (400 MHz, CDCl3): d=1.34 (d, 3J(H,H)=7.6 Hz, 1H; 13-H), 1.52 (d, 3J(H,H)=7.6 Hz, 1H; 14-H), 2.05–2.28 (m, 8H; 5-Ha, 5-Hb, 8-Ha, 8-Hb, 15-Ha, 15-Hb, 16-Ha, 16-Hb), 2.40–2.47 (m, 2H; 6-H, 7-H), 2.86 (d, 3J(H,H)=5.2 Hz, 1H; 2-H), 2.94 (br s, 1H; 3-H), 2.98 (br d, 3J(H,H)=4.4 Hz, 1H; 13a-H), 3.07–3.09 (m, 1H; 12a-H), 3.12–3.14 (m, 1H; 10-H), 3.19 (dd, 3J(H,H)=5.2, 3J(H,H)=4.8 Hz, 1H; 1-H), 3.65 (s, 3H; 2-COOCH3), 3.71 (s, 3H; 1-COOCH3), 6.25–6.26 ppm (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 11-H, 12-H]; 13C NMR (100.6 MHz, CDCl3): d=35.76 (CH) and 35.82 (CH) (C6 and C7), 39.6 (CH, C13), 40.1 (CH2) and 40.2 (CH2) (C8 and C16), 40.7 (CH2) and 41.0 (CH2) (C5 and C15), 43.6 (CH, C14), 44.4 (CH, C13a), 45.5 (CH, C3), 46.3 (CH, C12a), 46.6 (CH, C10), 49.3 (CH, C1), 49.6 (CH, C2), 51.97 (1-COOCH3), 51.98 (2-COOCH3), 123.6 (C, C9), 132.0 (C, C4), 132.9 (C, C3a), 138.3 (CH, C11), 138.5 (CH, C12), 140.2 (C, C9a), 173.2 (C, 1COOCH3), 173.9 ppm (C, 2-COOCH3); IR (ATR): n˜=2954 (w), 2914 (w), 2842 (w), 1723 (s), 1432 (m), 1306 (m), 1214 (m), 1190 (s), 1176 (s), 1163 (s), 1022 (m), 696 cm¢1 (m); accurate mass measurement: m/z calcd for C24H26O4+H+: 379.1904; found: 379.1910; elemental analysis calcd (%) for C24H26O4: C 76.17, H 6.92; found: C 76.11, H 6.93.

Analytical and spectroscopic data of compound 13: White solid; m.p. 191–1928C (EtOAc), at 184–1868C the sample of compound 13 becomes a paste; 1H NMR (400 MHz, CDCl3): d=1.93 (s, 2H; 13(14)-H), 2.09 (d, 2J(H,H)=12.8 Hz, 2H; 8(16)-Hb), 2.14 (d, 2J(H,H)= 12.4 Hz, 2H; 5(15)-Hb), 2.14–2.20 (m, 2H; 8(16)-Ha), 2.20–2.27 (m, 2H; 5(15)-Ha), 2.41–2.47 (m, 2H; 6(7)-H), 2.91 (dd, 3J(H,H)=2.4, 4J(H,H)=1.8 Hz, 2H; 3(13a)-H), 3.00 [dd, 3J(H,H)=2.4, 4J(H,H)= 1.8 Hz, 2H; 1(2)-H), 3.10 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 10(12a)-H), 3.64 (s, 6H; 2 OCH3), 6.25 ppm (pseudo t, 3J(H,H)= 4J(H,H)=2.0 Hz, 2H; 11(12)-H); 13C NMR (100.6 MHz, CDCl3): d=35.8 [CH, C6(7)], 38.1 [CH, C13(14)], 40.2 [CH2, C8(16)], 40.9 [CH2, C5(15)], 44.7 [CH, C3(13a)], 46.6 [CH, C10(12a)], 46.9 [CH, C1(2)], 51.4 (CH3, OCH3), 122.8 (C, C9), 130.8 (C, C4), 133.1 (C, C3a), 138.2 [CH, C11(12)], 141.6 (C, C9a), 172.4 ppm (C, COOCH3); IR (ATR): n˜= 2947 (w), 2919 (w), 2832 (w), 1746 (s), 1736 (s), 1442 (m), 1430 (m), 1354 (m), 1344 (m), 1193 (s), 1173 (s), 1159 (s), 1053 (m), 770 (m), 691 cm¢1 (m); accurate mass measurement: m/z calcd for C24H26O4+H+: 379.1904; found:

379.1907; elemental analysis calcd (%) for C24H26O4·0.25H2O: C 75.27, H 6.97; found: C 75.20, H 6.84.

Analytical and spectroscopic data of compound 14: White solid; m.p. 170–171 8C (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.41 (s, 2H; 13(14)-H), 2.09 (d, 2J(H,H)=12.8 Hz, 2H; 8(16)-Hb), 2.17 (d, 2J(H,H)= 12.8 Hz, 2H; 5(15)-Hb), 2.15–2.21 (m, 2H; 8(16)-Ha), 2.32–2.38 (m, 2H; 5(15)-Ha), 2.41–2.48 (m, 2H; 6(7)-H), 2.70 (s, 2H; 1(2)-H), 2.90 (s, 2H; 3(13a)-H), 3.13 (pseudo t, 3J(H,H)=4J(H,H)=1.8 Hz, 2H; 10(12a)-H), 3.58 (s, 6H; 2ÕOCH3), 6.28 ppm (t, 3J(H,H)=4J(H,H)= 1.8 Hz, 2H; 11(12)-H); 13C NMR (100.6 MHz, CDCl3): d=35.9 [CH, C6(7)], 40.2 [CH2, C8(16)], 40.9 [CH2, C5(15)], 43.7 [CH, C13(14)], 44.5 [CH, C3(13a)], 46.5 [CH, C10(12a)], 51.1 [CH, C1(2)], 51.6 (CH3, OCH3), 123.8 (C, C9), 131.7 (C, C3a), 133.6 (C, C4), 138.6 [CH, C11(12)], 139.6 (C, C9a), 172.7 ppm (C, COOCH3); IR (ATR): n˜=2992 (w), 2949 (m), 2919 (m), 2841 (m), 1745 (s), 1722 (s), 1433 (m), 1423 (m), 1347 (m), 1313 (m), 1275 (m), 1259 (s), 1164 (s), 1147 (s), 1023 (s), 767 (m), 752 (m), 742 (m), 703 cm¢1 (m); accurate mass measurement: m/z calcd for C24H26O4+H+: 379.1904; found: 379.1909; elemental analysis calcd (%) for C24H26O4·0.25H2O: C 75.27, H 6.97. Found: C 75.39, H 6.81.

Synthesis of the diester 10 from the diester 13

A suspension of the diester 13 (13 mg, 35 mmol) and 5% Pd on charcoal (50% in water, 2 mg) in EtOAc (10 mL) was hydrogenated at room temperature and atmospheric pressure for 2.5 h. The suspension was filtered through a short pad of celite and concentrated in vacuum to give the diester 10 (8 mg, 61% yield) as a white solid.

(1RS,2RS,3RS,3aZ,6SR,7RS,9Z,10RS,12aSR,13RS,13aSR,14SR)-1,2,5,6,7,8,10,12a,13,13a-decahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene-1,2-dicarboxylic acid (15)

An aqueous NaOH solution (9.6m, 7 mL) was added dropwise to a cold (0 8C, ice/water bath) suspension of a mixture of compounds 12, 13, and 14 (223 mg, 0.59 mmol) in 96% EtOH (2.4 mL), and then the mixture was heated at 958C for 4 h. The mixture was allowed to cool to room temperature, was acidified with 1n HCl and extracted with EtOAc (45 mL). The aqueous phase was extracted with EtOAc (2Õ40 mL). The combined organic phases were washed with water (2Õ20 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give a beige solid (205 mg, 92% yield), which was a stereoisomeric mixture, consisting mainly of the hydrated endo,exo-stereoisomer 15. M.p. 192–2018C (decomp.) (washed with hot EtOAc); 1H NMR (400 MHz, CD3OD): d=1.47 (d, 3J(H,H)=7.8 Hz, 1H; 13-H), 1.50 (d, 3J(H,H)=7.8 Hz, 1H; 14-H), 2.15–2.27 (m, 8H; 5-Ha, 5-Hb, 8-Ha, 8-Hb, 15-Ha, 15-Hb, 16-Ha, 16-Hb), 2.42–2.50 (m, 2H; 6-H, 7-H), 2.78 (d, 3J(H,H)=5.2 Hz, 1H; 2-H), 2.98 (br s, 1H; 3-H), 3.01 (br d, 3J(H,H)=4.4 Hz, 1H; 13a-H), 3.08–3.10 (m, 1H; 12a-H), 3.12 (dd, 3J(H,H)=5.2, 3J(H,H)=4.4 Hz, 1H; 1-H), 3.14–3.16 (m, 1H; 10-H), 6.25–6.27 ppm (pseudo t, 3J(H,H)=4J(H,H)= 2.0 Hz, 2H; 11-H, 12-H); 13C NMR (100.6 MHz, CD3OD): d=37.2 (CH) and 37.3 (CH) (C6 and C7), 40.82 (CH2) and 40.86 (CH2) (C8 and C16), 40.89 (CH, C13), 41.5 (CH2) and 41.7 (CH2) (C5 and C15), 45.2 (CH, C14), 45.5 (CH, C13a), 47.1 (CH, C3), 47.4 (CH, C12a), 47.8 (CH, C10), 50.6 (CH, C1), 51.0 (CH, C2), 124.3 (C, C9), 132.8 (C, C4), 134.8 (C, C3a), 139.28 (CH) and 139.34 (CH) (C11 and C12), 141.6 (C, C9a), 176.3 (C, 1-COOH), 177.1 ppm (C, 2-COOH); IR (ATR): n˜=3600–2300 (broad band, max. at 2939) (m), 1694 (s), 1408 (m), 1373 (m), 1235 (s), 1172 (s), 1042 (m), 717 (m), 687 cm¢1 (m); accurate mass measurement: m/z calcd for C22H22O4 ¢H¢: 349.1445; found: 349.1437; elemental analysis calcd (%) for C22H22O4·1.5H2O: C 70.01, H 6.68; found: C 69.66, H 6.58.

(2R,3S,5s,5ar,6R,8aS,9R,9aR,12S,12as,12bs,13S)-2,3,4,5,8a,9,9a-Octahydro-1H-6,9,12-(epimethanetriyl)-2,5:3,12b-dimethanocyclohepta[d]-s-indacen-12a(6H)-ol (16)

A solution of the diacid 15 (415 mg, 1.18 mmol) in pyridine (20 mL), water (2 mL), and Et3N (0.66 mL, 478 mg, 4.74 mmol) was electrolyzed by using two rectangular Pt electrodes (3.3Õ1.7 cm2) at a distance of 8 mm at 90 V (d.c., 0.34 A) in an open watercooled (20 8C) 50 mL vessel for 18 h. After 16 h, the current diminished till 0.06 A. Water (45 mL) and EtOAc (100 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2Õ100 mL). The combined organic phase and extracts were washed with 1n HCl (3Õ60 mL) and water (2Õ 60 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give a residue (165 mg), which was subjected to column chromatography (35–70 mm silica gel (4 g), pentane/EtOAc mixtures). On elution with pentane and pentane/EtOAc 95:5, the alcohol 16 (14 mg, 4% yield) was isolated as a beige solid. An analytical sample of compound 16 (8 mg) was obtained as a white solid by crystallization from EtOAc (1.2 mL). M.p. 108–1098C (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.40–1.48 (m, 4H; 1(15)-Hb, 4(14)-Ha), 1.55–1.58 (m, 2H; 4(14)-Hb), 1.59 (s, 2H; 9(13)-H), 1.85–1.91 (m, 2H; 1(15)-Ha), 2.33 (br s, 1H; O-H), 2.37–2.44 (m, 2H; 2(3)-H), 2.46 (m plus overlapped pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 3H; 5-H, 9a(12)-H), 2.55 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 6(8a)-H), 6.02 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 7(8)-H), 6.17 ppm (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 10(11)-H); 13C NMR (100.6 MHz, CDCl3): d=37.0 (CH, C5), 37.6 [CH, C2(3)], 40.7 [CH2, C1(15)], 41.6 [CH2, C4(14)], 48.2 [CH, C9(13)], 48.5 [CH, C6(8a)], 50.4 (C, C12b), 51.7 [CH, C9a(12)], 66.8 (C, C5a), 90.6 (C, C12a), 136.1 [CH, C7(8)], 136.4 ppm [CH, C10(11)]; IR (ATR): n˜=3500–3000 (broad band, w), 2950 (m), 2919 (s), 2850 (m), 1731 (m), 1456 (m), 1376 (m), 1319 (m), 1284 (m), 1274 (m), 1256 (m), 1163 (m), 1081 (m), 964 (m), 795 (m), 742 (s), 684 cm¢1 (s); accurate mass measurement: m/z calcd for C20H22O+NH4 +: 296.2009; found: 296.2012; elemental analysis calcd (%) for C20H22O2·0.25H2O: C 84.91, H 8.02; found: C 84.92, H 7.98.

(3R,3aZ,6s,7s,9Z,10S,12aR,13r,13aS,14r)-5,6,7,8,10,12a,13,13a-Octahydro-3H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene (17)

Glass powder (42 mg), 2,2'(-bipyridyl (749 mg, 4.80 mmol), and 97% Cu2O (708 mg, 4.80 mmol) were added to a solution of the diacid 15 (561 mg, 1.60 mmol) in quinoline (9.5 mL), and the mixture was heated at 1858C for 18 h. The mixture was allowed to cool to room temperature, poured onto 2n HCl (50 mL), filtered through a short pad of celite. and washed with water (15 mL) and pentane (100 mL). The organic phase was separated from the combined filtrate and the aqueous phase was extracted with pentane (3Õ100 mL). The combined organic phases were washed with 1n HCl (2Õ80 mL) and water (2Õ80 mL), dried with anhydrous Na2SO4, and distilled under atmospheric pressure by using a 10 cm Vigreux column and heating till 508C. The oily residue (59.5 mg) contained the tetraene 17, 2-methylnaphthalene, and traces of 1-methylnaphthalene and the alcohol 16. An approximate molar ratio of 17/2-methylnaphthalene of 1:2 was calculated from the integration of the signals corresponding to the olefinic protons of the tetraene 17 (d=6.37 ppm) and the methyl protons of 2-methylnaphthalene (d=2.51 ppm) in the 1H NMR spectrum of the mixture. This residue was placed in a desiccator containing paraffin wax under vacuum overnight to give the tetraene 17, containing traces of the alcohol 16 as a white solid (31 mg). The combined aqueous phases were extracted with EtOAc (3Õ100 mL) and the combined organic extracts were washed with 1n HCl (2Õ80 mL) and water (2Õ80 mL). The organic phase was extracted with a saturated aqueous NaHCO3 solution (3Õ80 mL) and water (2Õ80 mL). The organic phase was dried with anhydrous Na2SO4 and distilled under atmospheric pressure by using a 10 cm Vigreux column and heating till 110–1158C, to give an oily residue (127 mg) containing the tetraene 17, 2-methylnaphthalene, and traces of 1-methylnaphthalene and the alcohol 16 (approximate molar ratio 17/2-methylnaphthalene 2:1), which was subjected to column chromatography (neutral Al2O3 (8 g), pentane/EtOAc mixtures). On elution with pentane a first fraction (16 mg) consisting mainly of a mixture of 2-methylnaphthalene and the tetraene 17 in an approximate ratio 2-

methylnaphthalene/tetraene 17 of 8:1, and a second fraction (32 mg) consisting mainly of the tetraene 17 were isolated. The second fraction, after elimination of the methylnaphthalenes, as described before, gave pure the tetraene 17 (27 mg) as a white solid. On elution with pentane and pentane/EtOAc 9:1, a third fraction (6 mg) containing the impure alcohol 16 was isolated. The aqueous NaHCO3 extracts were acidified with 1n HCl (120 mL) and extracted with EtOAc (3Õ120 mL). The combined organic phases were washed with water (2Õ80 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give a solid residue (229 mg), which consisted mainly of the starting diacid 15. This product was resubmitted as such to the above-described bis-decarboxylation process leading to a pentane extract (15 mg) and an EtOAc extract (39 mg), both containing the tetraene 17, 2-methylnaphthalene, and the alcohol 16 in a 2-methylnaphthalene/tetraene 17/alcohol 16 ratio of about 4:2:1. These fractions were combined and subjected to column chromatography (neutral Al2O3 (7 g), pentane/ EtOAc mixtures). On elution with pentane, a mixture containing mainly 2-methylnaphthalene and the tetraene 17 (ratio 2-methylnaphthalene/tetraene 17 5:2, 6 mg) and the tetraene 17 (10.5 mg) were isolated. Altogether, the tetraene 17 (68.5 mg, 16% yield) was obtained as a white solid. A significant amount of 2-methylnaphthalene and traces of 1-methylnaphthalene and the alcohol 16 were also detected. An analytical sample of the tetraene 17 (8 mg) was obtained as a white solid by dissolving a fraction of 17 (11 mg) in pentane (3 mL) and allowing the solution to concentrate till a final volume of 0.5 mL. M.p. 164–1658C (pentane); 1H NMR (400 MHz, CDCl3): d=1.63 (s, 2H; 13(14)-H), 2.11 (d, 2J(H,H)= 12.4 Hz, 4H; 5(8,15,16)-Hb), 2.21 (m, 2J(H,H)=12.4 Hz, 3J(H,H)= 8.0 Hz, 4H; 5(8,15.16)-Ha), 2.43–2.49 (m, 2H; 6(7)-H), 2.97 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 4H; 3(10,12a,13a)-H), 6.37 ppm (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 4H, 1(2,11,12)-H); 13C NMR (100.6 MHz, CDCl3): d=36.6 [CH, C6(7)], 40.3 [CH2, C5(8,15,16)], 45.3 [CH, C3(10,12a,13a)], 46.2 [CH, C13(14)], 123.7 [C, C4(9)], 140.2 [CH, C1(2,11,12)], 141.0 ppm [C, C3a(9a)]; IR (ATR): n˜=2941 (m), 2919 (s), 2848 (m), 1445 (m), 1314 (m), 757 (m), 733 (m), 694 (m), 658 cm¢1 (m); accurate mass measurement: m/z calcd for C20H20+H+: 261.1638; found: 261.1643; elemental analysis calcd (%) for C20H20·0.1H2O: C 91.62, H 7.77; found: C 91.56, H 7.85.

(3R,3aZ,6s,7s,9Z,10S,12aR,13r,13aS,14r)-2,3,5,6,7,8,10,11,12,12a,13,13a-Dodecahydro-1H-3,10,13-(epimethanetriyl)-4,7:6,9-dimethanodicyclopenta[a,d][11]annulene (18)

5% Pd on charcoal (5 mg) was added to a solution of the tetraene 17 (13.6 mg, 52 mmol) in EtOAc (15 mL), and the mixture was stirred at room temperature under a hydrogen atmosphere (1 atm) for 1 h. The suspension was filtered through a short pad of Celite, the filtrate was concentrated in vacuum, and the residual beige solid was crystallized from EtOAc (1 mL) to give the diene 18 (10.2 mg, 74% yield) as a white solid. M.p. 171–172 8C (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.21–1.26 (m, 4H; 1(2,11,12)-Hx), 1.45–1.51 (m, 4H; 1(2,11,12)-Hn), 1.47 (s, 2H; 13(14)-H), 2.20 (d, 2J(H,H)=12.4 Hz, 4H; 5(8,15,16)-Hb), 2.26–2.30 (m, 4H; 5(8,15,16)- Ha), 2.38–2.44 (m, 2H; 6(7)-H), 2.41 ppm (pseudo t, 3J(H,H)= 4J(H,H)=2.0 Hz, 4H; 3(10,12a,13a)-H); 13C NMR (100.6 MHz, CDCl3): d=29.6 [CH2, C1(2,11,12)], 35.7 [CH, C6(7)], 41.0 [CH2, C5(8,15,16)], 41.4 [CH, C3(10,12a,13a)], 47.6 [CH, C13(14)], 128.2 [C, C4(9)], 137.7 ppm [C, C3a(9a)]; IR (ATR): n˜=2951 (s), 2935 (s), 2916 (s), 2860 (s), 2833 (s), 1436 (m), 1313 (m), 1298 (m), 1133 (m), 1108 (m), 936 (m), 816 (m), 781 (m), 742 (m), 652 cm¢1 (m); UV (n-pentane) lmax(e)=207 nm (1740 mol¢1m3cm¢1); UV (CH2Cl2) lmax(e)=228 nm (1750 mol¢1m3cm¢1); accurate mass measurement: m/z calcd for C20H24+H+: 265.1951; found: 265.1941; elemental analysis calcd (%) for C20H24: C 90.85, H 9.15; found: C 90.77, H 9.11.

(1R,3aS,4r,4aR,7S,7ar,9s,10s,11br,12r)-2,3,3a,4,4a,5,6,7,8,9,10,11-Dodecahydro-1H-1,4,7-(epimethanetriyl)-7b,10:9,11a-dimethanobenzo[3,4]cyclobuta[1,2 h]cyclopenta[a]pentalene (19)

Procedure a (in pentane): A solution of the diene 18 (10.4 mg, 39 mmol) in pentane (25 mL) was irradiated with a 125W mediumpressure mercury lamp for 3 h. At the end of the irradiation most of the solvent had been evaporated. The solution was concentrated to dryness in vacuum at room temperature, the residue was taken in CDCl3, and the different NMR spectra [1H and 13C NMR, DEPT, 1H/1H homocorrelation (gCOSY), 1H/13C heterocorrelation (one bond: gHSQC and long range: gHMBC)] were recorded at 258C. To check the ratio of compounds 18 and 19, several 1H NMR spectra were recorded at different times during the registration of the other spectra. From the spectra of a mixture of compounds 18 and 19, the 1H and 13C NMR data of compound 19 were obtained. 1H NMR (400 MHz, CDCl3): d=1.42–1.46 (br d, 2J(H,H)=8.8 Hz, 4H; 8(11,13,14)-Ha), 1.51–1.53 (overlapped d, 2J(H,H)=8.8 Hz, 4H; 8(11,13,14)-Hb), 1.52–1.56 (m, 8H; 2(3,5,6)-Hn, 2(3,5,6)-Hx), 1.59 (s, 2H; 4(12)-H), 2.24–2.26 (br s, 2H; 9(10)-H), 2.30 ppm (dd, 3J(H,H)= 2.4 Hz, 4J(H,H)=1.6 Hz, 4H; 1(3a,4a,7)-H); 13C NMR (100.6 MHz, CDCl3): d=25.3 [CH2, C2(3,5,6)], 39.4 [CH, C9(10)], 47.9 [CH2, C8(11,13,14)], 48.4 [C, C7b(11a)], 50.8 [CH, C4(12)], 54.2 [CH, C1(3a,4a,7)], 59.8 ppm [C, C7a(11b)].

Procedure b (in the solid state): A crystal of the diene 18 covert with Fomblin Y was mounted on a cryoloop supported on a goniometric bolster at about 4 cm from a 125 W low-pressure mercury lamp. The crystal was cooled at ¢1008C with a stream of cold nitrogen flowing from about 2 cm from the upper side of the crystal, while it was irradiated for 5 h. The crystal was rotated several times to irradiate it from different sites. After stopping the irradiation, the crystal was immediately submitted to X-ray diffraction analysis at 100 K (exposure time: 3.87 h). The X-ray data (see part 1.7 in the Supporting Information) show that the crystal contains molecules of the cyclobutane derivative 19 and the diene 18 in a ratio 19/18 of 1:1.

Thermal conversion of the cyclobutane 19 to the diene 18

The kinetics of the thermal conversion of compound 19 to compound 18 was followed by 1H NMR spectroscopy in CDCl3 at 25, 35, and 458C. The ratio 19/18 was obtained by integration of the signals at d=2.30 ppm corresponding to four protons (i.e. , 1(3a,4a,7)-H) of compound 19 and d=2.38–2.44 ppm (complex absorption) corresponding to six protons (i.e., 6(7)-H and 3(10,12a,13a)-H) of compound 18 (see Table S1 in the Supporting Information). The plots ln[%19] versus time for each temperature gave straight lines (first-order kinetics) (r2=0.99, n=4 for the process at 25 8C, r2=0.98, n=10 for the process at 358C, and r2=0.99, n=7 for the process at 458C) with rate constant values of k25= 0.0030, k35=0.0112, and k45=0.0231 min¢1. From these rate constant values, by using the Arrhenius equation, approximate values for the activation energy (19.2 kcalmol¢1) and the pre-exponential Arrhenius factor (3.4Õ1011 min¢1) were calculated.

(2R,3S,5s,5as,6S,8aR,9R,9aS,12R,12as,12br,13S)-5,12a-Dibromo-2,3,4,5,6a,7,8,8a,9,9a,10,11,12a,12b-tetradecahydro-1H-6,9,12-(epimethanetriyl)-2,5:3,12b-dimethanocyclohepta[d]-s-indacene (21)

A 0.49m solution of Br2 [0.1 mL, 49 mmol, prepared by dissolving Br2 (50 mL) in CH2Cl2 (2 mL)] was added dropwise to a stirred solution of the diene 18 (11.1 mg, 42 mmol) in anhydrous CH2Cl2 (2 mL) under an Ar atmosphere, and the reaction mixture was stirred at room temperature protected from light for 20 h. The brown solution was diluted with CH2Cl2 (5 mL), washed with a 10% aqueous solution of NaHSO3 (1Õ3 mL plus 2Õ2.5 mL) and water (3 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give the crude dibromo derivative 21 as a light brown solid (19.8 mg), which was crystallized from EtOAc (3 mL) to give compound 21 (16 mg, 89% yield) as a white solid. M.p.

260–261 8C (decomp.) (EtOAc); 1H NMR (400 MHz, CDCl3): d=1.03–1.08 (m, 2H; 7(8)-Hn), 1.17–1.22 (m, 2H; 10(11)-Hn), 1.59–1.63 (m, 2H; 1(15)-Hb), 1.60 (overlapped s, 2H; 9(13)-H), 1.94–2.00 (m, 2H; 10(11)-Hx), 2.17–2.23 (m, 2H; 1(15)-Ha), 2.20 (overlapped pseudo t, 3J(H,H)=4J(H,H)= 2.0 Hz, 2H; 9a(12)-H), 2.23 (overlapped dd, 3J(H,H)=2.4, 4J(H,H)= 2.0 Hz, 2H; 6(8a)-H), 2.24–2.30 (m, 2H; 4(14)-Ha), 2.33–2.38 (m, 2H; 4(14)-Hb), 2.39–2.44 (m, 2H; 2(3)-H), 2.63–2.69 ppm (m, 2H; 7(8)-Hx); 13C NMR (100.6 MHz, CDCl3): d=29.4 [CH2, C10(11)], 30.0 [CH2, C7(8)], 38.9 [CH, C2(3)], 44.26 [CH, C6(8a)], 44.35 [CH2, C1(15)], 49.2 [CH, C9a(12)], 52.1 [CH, C9(13)], 55.6 (C, C12b), 56.2 [CH2, C4(14)], 65.9 (C, C5a), 67.4 (C, C5), 88.0 ppm (C, C12a); IR (ATR): n˜=2956 (m), 2936 (m), 2883 (w), 2863 (w), 1460 (m), 1442 (w), 1311 (w), 1300 (w), 1123 (w), 1098 (w), 988 (w), 954 (s), 923 (m), 899 (m), 839 (w), 786 (m), 698 cm¢1 (s); accurate mass measurement: m/z calcd for C20H24 79Br2 ¢Br+: 343.1055; found: 343.1064; elemental analysis calcd (%) for C20H24Br2: C 56.63, H 5.70; found: C 57.15, H 6.05.

(2R,3S,5s,5as,6S,8aR,9R,9aS,12R,12as,12br,13S)-5,12a-Diiodo-2,3,4,5,6a,7,8,8a,9,9a,10,11,12a,12b-tetradecahydro-1H-6,9,12-(epimethanetriyl)-2,5:3,12b-dimethanocyclohepta[d]-s-indacene (22)

Iodine (18 mg, 71 mmol) was added to a stirred solution of the diene 18 (11.3 mg, 43 mmol) in anhydrous CH2Cl2 (2 mL) under an Ar atmosphere, and the reaction mixture was stirred at room temperature protected from light for 20 h. The brown solution was diluted with CH2Cl2 (6 mL), washed with a 10% aqueous solution of NaHSO3 (1Õ5 mL plus 2Õ4 mL) and water (4 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give the crude diiodo derivative 22 as a light brown solid (26 mg), which was treated with hot EtOAc (3 mL) to give compound 22 (14 mg, 61% yield) as a white solid. M.p. 232–2338C (decomp.), at 1958C the sample of compound 22 became brown); 1H NMR (400 MHz, CDCl3): d=1.00–1.05 (m, 2H; 7(8)-Hn), 1.17–1.22 (m, 2H; 10(11)-Hn), 1.54 (s, 2H; 9(13)-H), 1.67–1.72 (m, 2H; 1(15)-Hb), 1.90–1.96 (m, 2H; 10(11)-Hx), 2.18–2.23 (m, 4H; 2(3)-H, 1(15)-Ha), 2.22 (overlapped pseudo t, 3J(H,H)=4J(H,H)=2.4 Hz, 2H; 6(8a)-H), 2.28 (dd, 3J(H,H)= 2.4, 4J(H,H)=1.6 Hz, 2H; 9a(12)-H), 2.53–2.58 (m, 4H; 4(14)-Ha, 4(14)-Hb), 2.82–2.89 ppm (m, 2H; 7(8)-Hx); 13C NMR (100.6 MHz, CDCl3): d=29.2 [CH2, C7(8)], 31.4 [CH2, C10(11)], 40.6 [CH, C2(3)], 44.0 [CH, C6(8a)], 44.3 (C, C5), 47.8 [CH2, C1(15)], 50.7 [CH, C9a(12)], 51.4 [CH, C9(13)], 56.1 (C, C12b), 61.2 [CH2, C4(14)], 64.9 (C, C5a), 82.1 ppm (C, C12a); IR (ATR): n˜=2951 (m), 2925 (m), 2888 (w), 2863 (w), 1454 (m), 1439 (w), 1294 (w), 1192 (w), 1121 (m), 1114 (m), 949 (m), 927 (w), 914 (w), 892 (m), 835 (w), 783 (m), 681 cm¢1 (s); accurate mass measurement: m/z calcd for C20H24I2 ¢I+: 391.0917; found: 391.0904; elemental analysis calcd (%) for C20H24I2·H2O: C 44.80, H 4.89; found: C 44.55, H 4.86.

Dimethyl (2R,3S,5s,5ar,6R,7S,8R,8aS,9S,9aS,12-R,12as,12br,13R)-5,12a-dibromo-2,3,4,5,6a,7,8,8a,9,9a,10,11,12a,12b-tetradecahydro-1H-6,9,12-(epimethanetriyl)-2,5:3,12b-dimethanocyclohepta[d]-s-indacene-7,8-dicarboxylate (23) and dimethyl (2R,3S,5s,5as,6R,8aS,9R,9aS,10S,11R,12R,12ar,12br,13S)-5,12adibromo-2,3,4,5,6a,7,8,8a,9,9a,10,11,12a,12b-tetradecahydro-1H-6,9,12-(epimethanetriyl)-2,5:3,12b-dimethanocyclohepta[d]-s-indacene-10,11-dicarboxylate (24)

Bromine (30 mL, 94 mg, 0.58 mmol) was added to a stirred solution of the diester 10 (158 mg, 0.41 mmol) in CH2Cl2 (2 mL) under an Ar atmosphere, and the solution protected from light was stirred at room temperature for 21 h. To the brown solution, a 10% aqueous Na2S2O3 solution (4 mL) and CH2Cl2 (5 mL) were added. The organic phase was separated, washed with a 10% aqueous Na2S2O3 solution (2Õ4 mL) and water (2Õ3 mL), dried with anhydrous Na2SO4, and concentrated in vacuum to give a white residue (211 mg, 95% yield), which was a mixture of compounds 23 and 24 in a ratio close

to 3.5:1 (determined by 1H NMR spectroscopy). Slow crystallization from EtOAc (2 mL) gave the main isomer 23 as colorless prisms (88 mg). The mother liquors were concentrated to dryness and the residue, still enriched with the main stereoisomer, was crystallized from EtOAc (5 mL) to give colorless needles corresponding to the minor stereoisomer 24 (14 mg). Further crystallization of the mother liquors gave more compound 24 (11 mg).

Analytical and spectroscopic data of compound 23: Colorless prisms; m.p. 230–231 8C (EtOAc); 1H NMR (400 MHz, CDCl3): d= 1.23–1.28 (m, 2H; 10(11)-Hn), 1.58–1.62 (m, 2H; 1(15)-Hb), 1.95–1.99 (m, 2H; 10(11)-Hx), 2.20 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 9a(12)-H), 2.22–2.30 (m, 2H; 1(15)-Ha), 2.27 (s, 2H; 9(13)-H), 2.31–2.37 (m, 2H; 4(14)-Ha), 2.41 (d, 2J(H,H)=10.8 Hz, 2H; 4(14)-Hb), 2.43–2.47 (m, 2H; 2(3)-H), 2.65 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 6(8a)-H), 3.65 (s, 6H; 2 OCH3), 4.45 ppm (pseudo t, 3J(H,H)= 4J(H,H)=2.0 Hz, 2H; 7(8)-H); 13C NMR (100.6 MHz, CDCl3): d=29.3 [CH2, C10(11)], 39.0 [CH, C2(3)], 44.3 [CH2, C1(15)], 44.4 [CH, C9(13)], 44.9 [CH, C7(8)], 47.5 [CH, C6(8a)], 48.7 [CH, C9a(12)], 51.5 (CH3, OCH3), 56.2 (C, C12b), 56.7 [CH2, C4(14)], 66.0 (C, C5a), 67.9 (C, C5), 86.8 (C, C12a), 172.8 ppm (C, COOCH3); IR (ATR): n˜=2948 (m), 2875 (w), 1735 (s), 1731 (s), 1460 (m), 1434 (m), 1344 (m), 1204 (s), 1191 (s), 1168 (s), 1098 (m), 1065 (m), 1047 (m), 936 (m), 899 (m), 699 cm¢1 (s); accurate mass measurement: m/z calcd for C24H28 79Br2O4+H+: 539.0427; found: 539.0437; elemental analysis calcd (%) for C24H28Br2O4: C 53.35, H 5.22, Br 29.58; found: C 53.32, H 5.33, Br 29.62.

Analytical and spectroscopic data of compound 24: Colorless needles; m.p. 251–252 8C (EtOAc); 1H NMR (400 MHz, CDCl3): d= 1.11–1.16 (m, 2H; 7(8)-Hn), 1.60–1.63 (m, 2H; 1(15)-Hb), 2.17 (s, 2H; 9(13)-H), 2.16–2.23 (m, 2H; 1(15)-Ha), 2.24–2.30 (m, 2H; 4(14)-Ha), 2.25 (t, J=2.0 Hz, 2H, 6(8a)-H), 2.35 (d, J=11.2 Hz, 2H, 4(14)-Hb), 2.40–2.45 (m, 2H, 2(3)-H), 2.54 (t, J=2.0 Hz, 2H, 9a(12)-H), 2.64–2.71 (m, 2H, 7(8)-Hx), 3.60 (pseudo t, 3J(H,H)=4J(H,H)=2.0 Hz, 2H; 10(11)-H), 3.66 ppm (s, 6H; 2 OCH3); 13C NMR (100.6 MHz, CDCl3): d=29.9 [CH2, C7(8)], 38.9 [CH, C2(3)], 44.1 [CH, C6(8a)], 44.3 [CH2, C1(15)], 45.9 [CH, C9(13)], 46.4 [CH, C10(11)], 51.6 (CH3, OCH3), 52.0 [CH, C9a(12)], 55.3 (C, C12b), 56.1 [CH2, C4(14)], 66.4 (C, C5), 66.6 (C, C5a), 87.3 (C, C12a), 172.2 ppm (C, COOCH3); IR (ATR): n˜=2956 (m), 2941 (m), 2886 (w), 1742 (s), 1731 (s), 1435 (m), 1337 (m), 1306 (m), 1205 (s), 1175 (s), 1158 (s), 1134 (m), 1048 (m), 955 (m), 933 (m), 894 (m), 710 (s), 681 cm¢1 (m); accurate mass measurement: m/z calcd for C24H28 79Br2O4+H+: 539.0427; found: 539.0414; elemental analysis calcd (%) for C24H28Br2O4·0.25H2O: C 52.91, H 5.27, 29.58; found: C 52.79, H 5.12, Br 29.28.

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Legends to figures

Scheme 1. Generation and dimerization of the highly pyramidalized alkenes 2 and several transformations of the diene dimers 4.

Scheme 2. Preparation of the domino DA adducts 8 and 9 and their derivatives.

Scheme 3. Preparation of the tetraene 17 (d.c.=direct current).

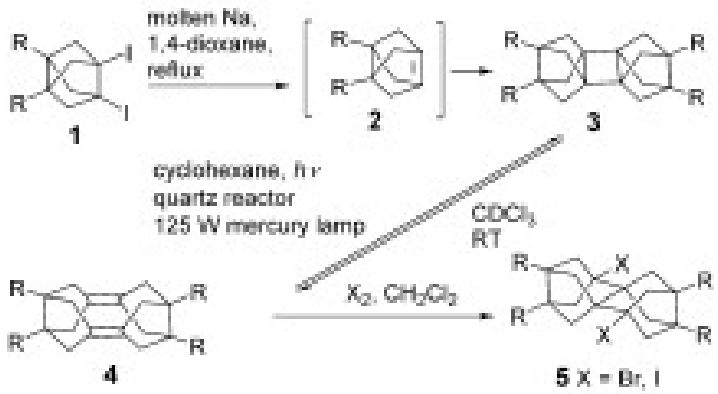
Scheme 4. Transannular reactions of compounds 18 and 10.

Figure 1. ORTEP representation of the mixture of the cyclobutane 19 and the diene 18.

Figure 2. Mechanistic pathway for the bromination of the diene 18 and formation of the N-type product 21.

Figure 3. Molecular geometry and selected properties of the brominated cation adducts derived from the diene 18. Representation of the two Ntype- brominated adduct cations and the single U-type addition product obtained from M062X calculations (the relative stability in [kcalmol¢1] is given in parenthesis). The length of the central bond (in [æ]) and the electron density at the bond critical point (in units of electron) is given above/below the bond, respectively.

SCHEME 1.

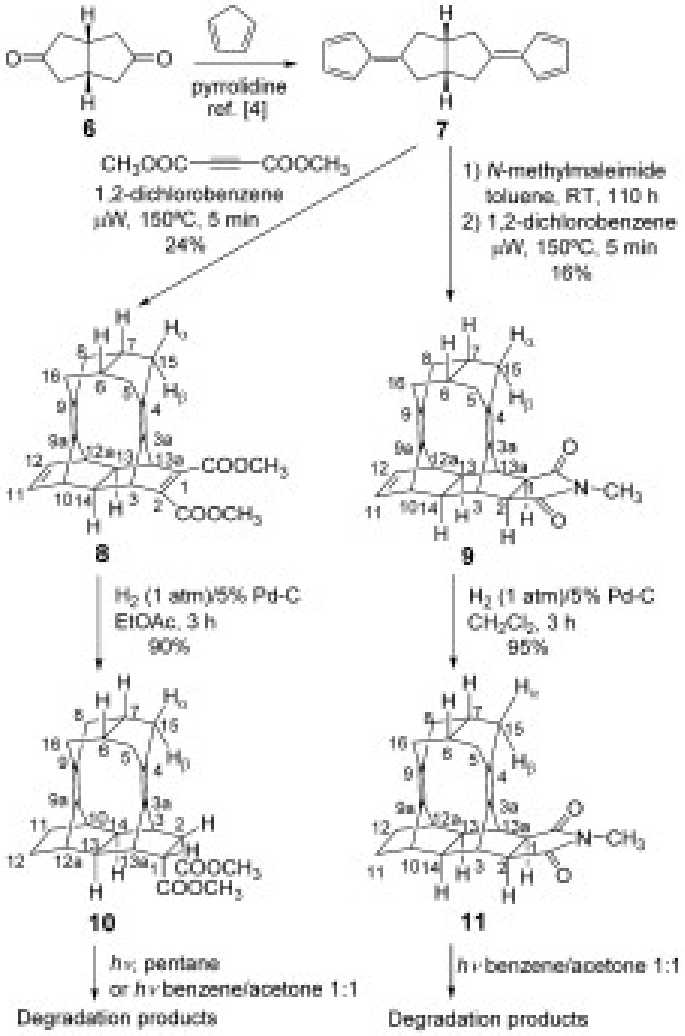


1-4a: R = Me; **1-4b**: R = H; **1-4c**: R,R = CH_2O-$C(Me_2)$-OCH_2;
1-2,4d: R,R = O-$C(Me)_2$-O; **1-2,4,5e**: R,R = CH_2OCH_2.

738 **SCHEME 2.**

739

740



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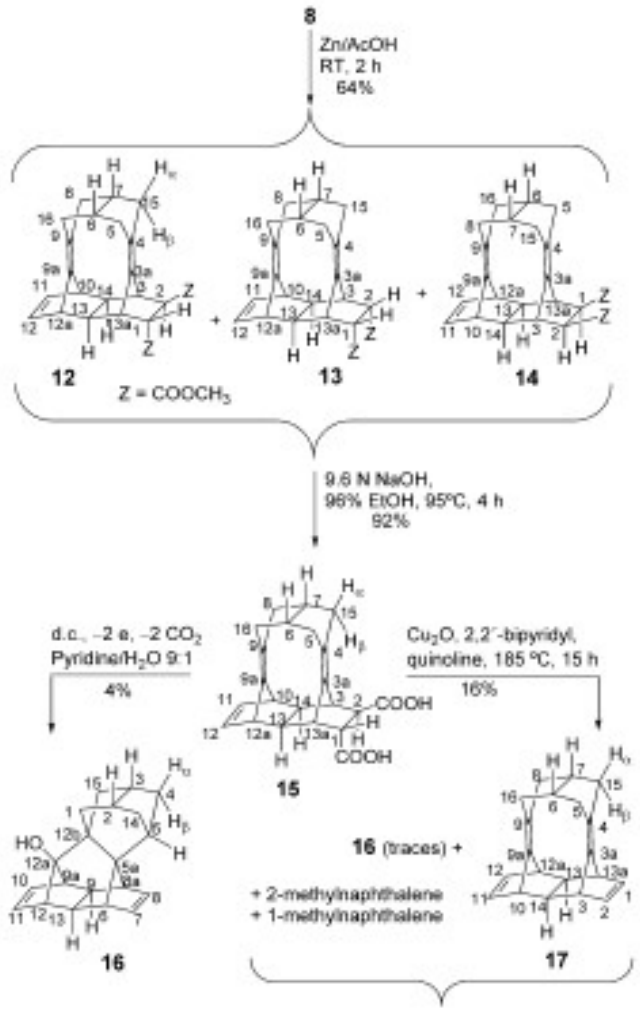
743 **SCHEME 3**

744

745



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748 **SCHEME 4**

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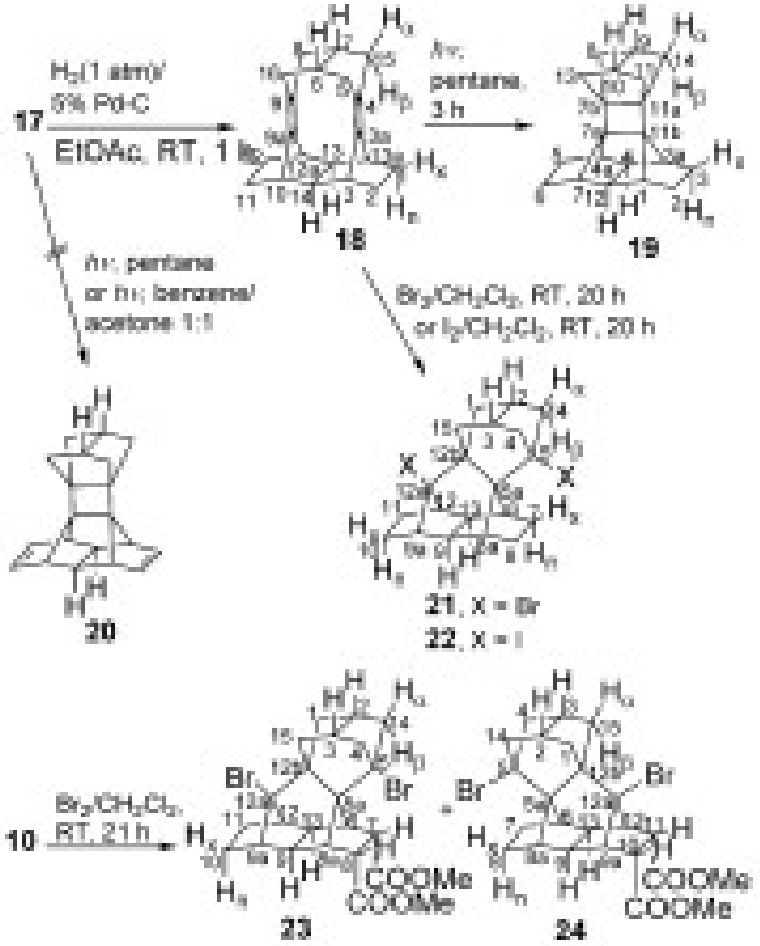
750



751

752

FIGURE 1.

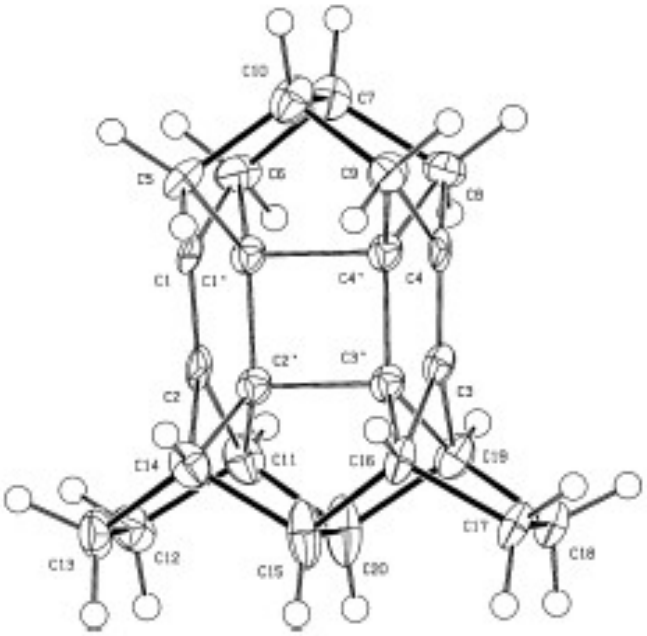

C10
C7
C5
C6
C9
C8
C1
C1*
C4*
C4
C2*
C3*
C2
C3
C14
C11
C16
C19
C17
C18
C13
C12
C15
C20

FIGURE 2.

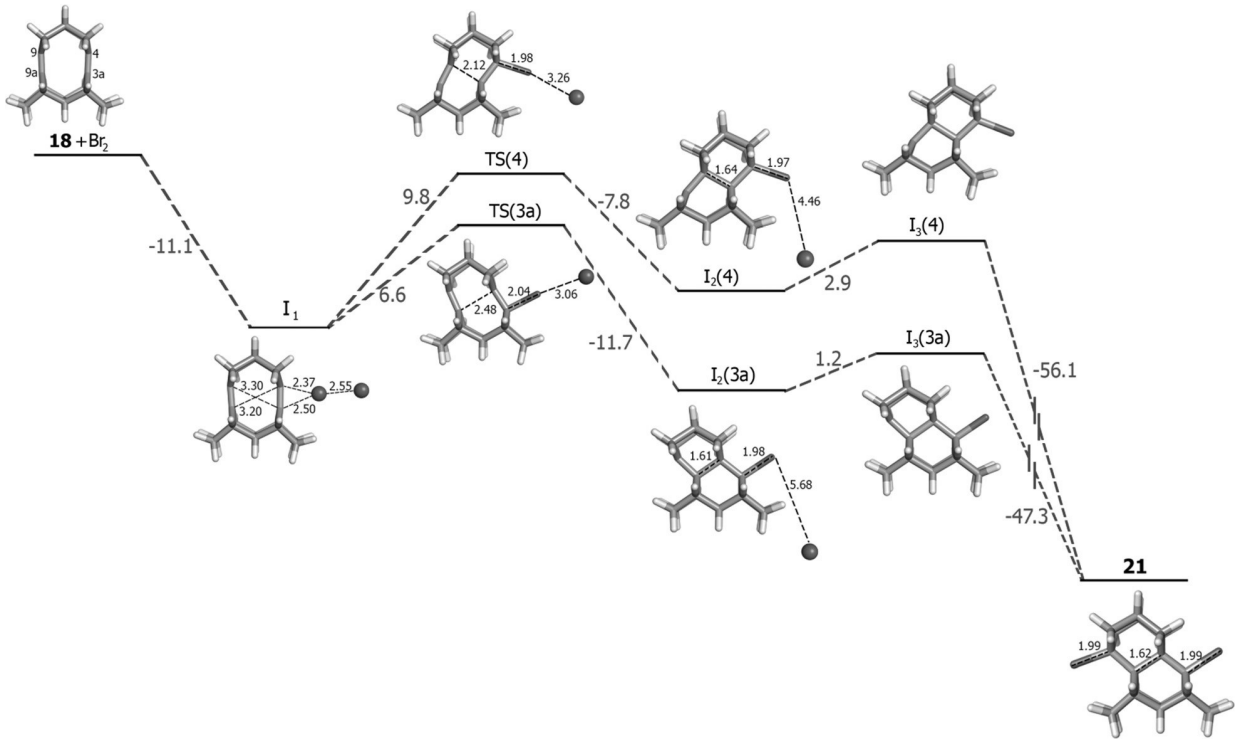
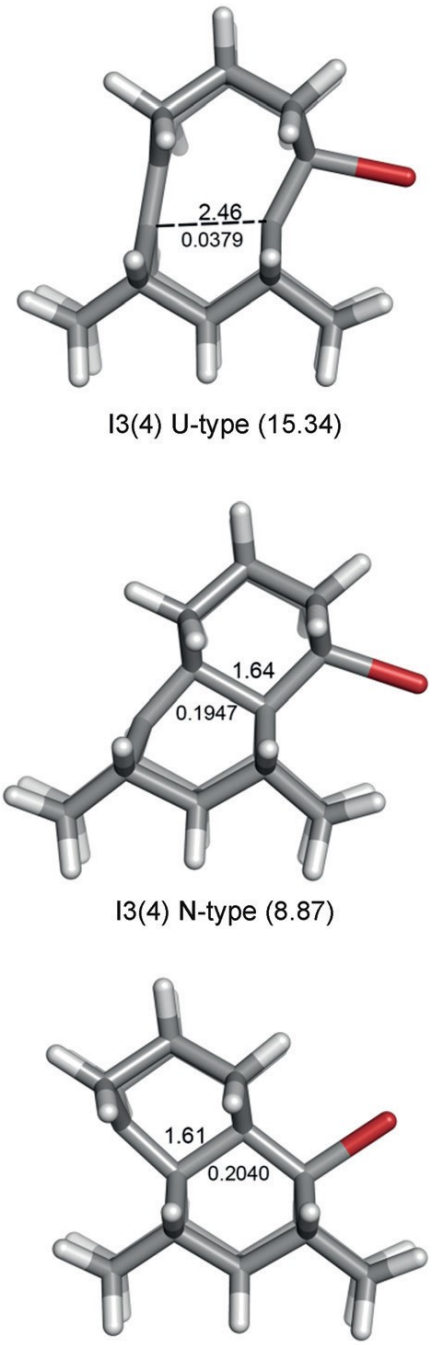

9
4
9a
3a
18 + Br2
-11.1
I1
3.30
2.37
2.55
3.20
2.50
9.8
TS(4)
2.12
1.98
3.26
6.6
TS(3a)
2.48
2.04
3.06
-7.8
I2(4)
1.64
1.97
4.46
2.9
I3(4)
-11.7
I2(3a)
1.61
1.98
5.68
1.2
I3(3a)
-56.1
-47.3
21
1.99
1.62
1.99

FIGURE 3.


2.46
0.0379
I3(4) U-type (15.34)
1.64
0.1947
I3(4) N-type (8.87)
1.61
0.2040
I3(3a) N-type (0.00)